Regimen Monograph

A - Regimen Name

PEME Regimen

Pemetrexed

Disease Site	Lung - Mesothelioma
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

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B - Drug Regimen

pemetrexed	500 mg /m²	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Premedication:

- Vitamin supplementation starting ≥ 1 week prior to first pemetrexed dose; continue until 3 weeks after last dose to reduce treatment-related toxicities:
  - Folic acid 0.4 mg - 1 mg PO daily
  - Vitamin B_{12} 1000 mcg IM q9 weeks
- Dexamethasone (e.g. 4 mg PO BID) beginning on the day before chemotherapy for a total of 3 days to reduce the incidence and severity of cutaneous reactions.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

- NSAIDs should be held for at least 2-5 days prior to, and at least 2 days after pemetrexed infusion (see Interactions section).
- Patients should not begin a new treatment cycle unless:
  - ANC ≥ 1.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Creatinine clearance is ≥ 45 mL/min

Dosage with toxicity

Hematologic:

Worst toxicity in previous cycle	Grade	Pemetrexed (% previous dose)*
Thrombocytopenic bleeding		50%

ANC	Grade 4	75%
Platelets	≥ Grade 3	
Recurrent myelosuppression after 2 dose reductions	≥ Grade 3	Discontinue

*Start next cycle only when ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and related organ/non-hematologic toxicity ≤ grade 2 (or recovery to baseline).

Non-hematologic:

Worst toxicity in previous cycle	Grade	Pemetrexed (% previous dose)*
Neurotoxicity	Grade 2	100%
	≥ Grade 3	Discontinue
Mucositis	≥ Grade 3	50%
Diarrhea	≥ Grade 3 or requiring hospitalization	75%
Pneumonitis	Any	Hold and investigate; discontinue if confirmed
All other related organ / non-hematologic toxicity	Grade 3	75%
	Grade 4	Discontinue
Stevens-Johnson syndrome	Any	
Toxic epidermal necrolysis		
Recurrent non-hematologic toxicity after 2 dose reductions	≥ Grade 3	

*Start next cycle only when ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and related organ/non-hematologic toxicity ≤ grade 2 (or recovery to baseline).

Hepatic Impairment

Pemetrexed is not extensively metabolized in the liver. No specific studies have been performed in patients with moderate or severe hepatic impairment. Pemetrexed should be used with caution in patients with hepatic impairment.

Renal Impairment

Use with caution as pemetrexed exposure is increased in renal impairment.

Creatinine clearance	Pemetrexed (% of previous dose)

(mL/min)	
≥ 45	100%*
< 45	Discontinue

* Exercise caution with co-administration of NSAIDs for patients with CrCl 45-79mL/min

Dosage in the Elderly

No dose adjustments are needed but patients should be monitored closely. In maintenance therapy, more frequent myelosuppression, renal and severe GI adverse events were noted in patients ≥ 65 years of age. There was no observed effect of age on pemetrexed pharmacokinetics over the range of 26 to 80 years.

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F - Adverse Effects

Refer to pemetrexed drug monograph(s) for additional details of adverse effects

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Fatigue • Nausea, vomiting	• Anorexia • Mucositis (including esophagitis, may be severe) • Myelosuppression ± infection, bleeding • Rash (may be severe) • Diarrhea (may be severe) • ↑ LFTs (may be severe)	• Neuropathy • Eye disorders (including conjunctivitis and increased lacrimation) • Creatinine increased • Arrhythmia • Arterial / venous thromboembolism • GI perforation • Hypersensitivity • Radiation recall reaction • Hemolysis • Pneumonitis

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G - Interactions

Refer to pemetrexed drug monograph(s) for additional details

- Hold NSAIDs with short half-lives (eg. ibuprofen) for at least 2 days before to at least 2 days after pemetrexed administration in patients with mild to moderate renal impairment (CrCl 45–79 mL/min).
- Hold NSAIDs with long half-lives (eg. piroxicam) for at least 5 days before to at least 2 days after pemetrexed administration.

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H - Drug Administration and Special Precautions

Refer to pemetrexed drug monograph(s) for additional details.

Administration:

- Reconstitute as directed with Normal Saline (preservative free).
- Dilute drug to a total volume of 100mL with normal saline only and infuse intravenously over 10 minutes.

- Reconstituted solution maybe colourless to yellow or green-yellow.
- Incompatible with calcium-containing solutions.
- Do not co-administer with other drugs and diluents.
- Keep unopened vials at room temperature. Pemetrexed is not light sensitive.

Contraindications:

- Patients with a known hypersensitivity to the drug/excipients.
- Concomitant use of yellow fever vaccine.

Other Warning/Precautions:

- Exercise caution in patients with pre-existing cardiovascular risk factors.
- Patients with moderate-severe renal dysfunction (CrCl < 45 mL/min).
- Avoid the use of live or live-attenuated vaccines.

Pregnancy/Lactation

- Pemetrexed is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.
- Pemetrexed may cause irreversible infertility.
    - Sperm preservation should be considered prior to starting treatment in males.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline, before each cycle, on days 8 and 15 of each cycle (for nadir and recovery), and as clinically indicated
- Liver function tests; baseline and at each visit
- Renal function tests; baseline and at each visit
- Clinical toxicity assessment for fatigue, pneumonitis, thromboembolism, mucositis, diarrhea, neurotoxicity, infection, bleeding and rash; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	21.349 minutes
Nursing Workload (average time per visit)	36.667 minutes

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K - References

Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin Oncol 2008;26(10):1698-704.

Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemonaïve and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. J Thorac Oncol 2008;3(7):764-71.

Pemetrexed drug monograph, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer
- Endorsement of the 2018 ASCO Treatment of Malignant Pleural Mesothelioma Guideline

June 2021 removed "unfunded" flag from pemetrexed

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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